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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,069	04/10/2001	Marschall S. Runge	CLFR:183US	8710

7590 02/15/2005

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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 02/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/832,069

Applicant(s)

RUNGE ET AL.

Examiner

Jeanine A Goldberg

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 6-9 and 14-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6-9 and 14-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed December 6, 2004. Currently, claims 6-9, 14-23 are pending.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 6, 2004 has been entered.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

It is noted that no IDS has been filed and applicants did not respond to the notice.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1634

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 6, 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using QPCR, does not reasonably provide enablement for detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using

Art Unit: 1634

QPCR, detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches that tissue ischemia, OXPHOS gene defects, environmental toxins, mtDNA mutations, decreased cellular ATP and oxygen radical formation all affect oxidative phosphorylation dysfunction which leads to tissue degeneration and cell death (Corral-Debrinski et al. 1992). The art does not teach how the amount of mtDNA damage is affected or associated by each of these factors.

Guidance in the Specification.

The specification states “a person having ordinary skill in this art would recognize that measurement of mitochondrial DNA damage is only one potential method to determine oxidative stress. Any downstream or resultant effect of mitochondrial DNA damage will reflect the same disease process. For example, measurement of mitochondrial protein production, changes in mitochondrial ATP production would accomplish the same goal. The specification provides no evidence teachings regarding the relationship between mtDNA damage and mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not teach how

these measurements are associated. A mutation in mtDNA may cause such problems with the mtDNA damage that there is no protein production, for example. Thus, measuring protein production of zero due to a truncation mutation would not provide any guidance of the quantity of DNA damage. Since only one mutation may completely negate the protein production, it is unpredictable that this would provide the skilled artisan with the amount of mtDNA damage present. Alternatively, the lesions or mutations/damage may occur in non-coding regions which do not affect protein. The specification has not taught that there is any direct tie. Similarly, the specification does not provide any links between mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Reduced ATP could be a single lesion and not due to a larger number of quantitative lesions in the genome. The knockout of mitochondrial enzyme with a single mutation could cause dysfunction.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try.

Working Examples

The specification has no working examples of measuring the *amount* of mtDNA damage in tissue using mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. As discussed above,

Art Unit: 1634

there is no guidance or teachings in the specification how measurements of the amount of mtDNA damage in a tissue is associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. There are many other factors which would affect each of these quantities which may not be related to amount of mtDNA damage. Further, there may be several serious mutations which would dramatically affect mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state which would not allow for quantification of mtDNA damage using mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art does not teach how the amount of mtDNA in a tissue may be associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research

required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 7 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 7 has been amended to depend upon Claim 15. Claim 15, 14, and 6 no longer recite "nuclear gene." Nuclear gene lacks proper antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 6, 23 are rejected under 35 U.S.C. 102(b) as being anticipated by VenMurthy et al. (Acta Biochimica Polonica, Vol. 43, No. 1, pages 227-240, 1996).

VenMurthy teaches studying the vulnerability of the mitochondrial genome to oxidative stress (page 233, col. 1). VenMurthy teaches that because of their high reactivity and short life, the hydroxyl radicals produced in mitochondria would be expected to produce deleterious effects mainly in this organelle (page 234, col. 1). VenMurthy teaches that the spontaneous mutation rate of mtDNA is considerably higher than that of nDNA. VenMurthy teaches that a variety of chronic degenerative diseases that affect the brain, heart, muscle, kidney and endocrine glands have been shown to result from mutations in mtDNA including LHON, MERRF, MELAS, and fatal infantile cardiomyopathy. VenMurthy also teaches that a variety of more common degenerative disorders such as heart disease, adult-onset Alzheimer's disease and aging, may also be related to mtDNA mutations (page 235, col. 1). VenMurthy specifically teaches investigation of mtDNAs isolated from blood lymphocytes from patients. VenMurthy teaches that blood cells represent the most accessible and most readily available of human tissues. VenMurthy teaches that they exist in continuous and intimate contact with the dyslipidemic plasma and their mtDNA would therefore be expected to show any damage resulting from the abnormal environment in their milieu (page 236, col. 1). VenMurthy teaches lymphocytes are selected for their abundance, their mitochondrial content and certain special features of their metabolism. VenMurthy teaches that deletions and insertions in mtDNA was carried out by PCR amplification of consecutive overlapping regions of mtDNA.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 6, 7, 8, 9, 14, 15, 21, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of VenMurthy et al. (Acta Biochimica Polonica, Vol. 43, No. 1, pages 227-240, 1996).

The instant specification defines "oxidative stress" to refer to pathophysiological effects of reactive oxygen species, such as H₂O₂, superoxide, peroxynitrate, and other reactive oxygen species (page 25 of the specification).

Yan et al. (herein referred to as Yan) teaches in vivo evidence of the relationship of reactive oxygen species and mitochondrial DNA damage in atherosclerosis. Specifically, Yan teaches assaying both diseased and normal human aortic tissues for DNA damage using a gene-specific quantitative PCR assay. Yan teaches designing primers to amplify a fragment of the human mitochondrial genome and a nuclear fragment within the beta-globin gene. Fresh surgical specimens of normal and atherosclerotic human aorta were immediately frozen in liquid nitrogen. Yan reports that mtDNA damage detected in atherosclerotic tissue was 2 to 5 fold higher than that of human aortic samples without evidence of atherosclerosis. The evidence suggest that the average DNA lesion frequency in the mitochondrial genome was approximately four

Art Unit: 1634

times higher than that in the nuclear B-globin gene (limitations of Claim 6, 7, 8). Yan teaches that the levels of H₂O₂ and O₂⁻ were assessed using a peroxidase-H₂O₂ formation assay. The results of Yan suggest that an increase in H₂O₂ and O₂⁻ levels in patients with CAD compared to those without CAD, consistent with a correlation between mtDNA damage and ROS generation. Yan teaches that the data suggest that oxidative mtDNA damage may play a role in atherosclerotic lesion development.

Yan does not specifically teach using a hematopoietic tissue, such as a white cell (limitations of Claim 23).

However, VenMurthy teaches studying the vulnerability of the mitochondrial genome to oxidative stress (page 233, col. 1). VenMurthy teaches that because of their high reactivity and short life, the hydroxyl radicals produced in mitochondria would be expected to produce deleterious effects mainly in this organelle (page 234, col. 1). VenMurthy teaches that the spontaneous mutation rate of mtDNA is considerably higher than that of nDNA. VenMurthy teaches that a variety of chronic degenerative diseases that affect the brain, heart, muscle, kidney and endocrine glands have been shown to result from mutations in mtDNA including LHON, MERRF, MELAS, and fatal infantile cardiomyopathy. VenMurthy also teaches that a variety of more common degenerative disorders such as heart disease, adult-onset Alzheimer's disease and aging, may also be related to mtDNA mutations (page 235, col. 1). VenMurthy specifically teaches investigation of mtDNAs isolated from blood lymphocytes from patients. VenMurthy teaches that blood cells represent the most accessible and most readily available of human tissues. VenMurthy teaches that they exist in continuous and intimate contact

Art Unit: 1634

with the dyslipidemic plasma and their mtDNA would therefore be expected to show any damage resulting from the abnormal environment in their milieu (page 236, col. 1).

VenMurthy teaches lymphocytes are selected for their abundance, their mitochondrial content and certain special features of their metabolism. VenMurthy teaches that deletions and insertions in mtDNA was carried out by PCR amplification of consecutive overlapping regions of mtDNA.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified mitochondrial damage by comparing the amount of damage in patient and control samples using blood, as taught by VenMurthy. VenMurthy specifically teaches the benefit of using blood samples, such as white blood cells (i.e. lymphocytes). VenMurthy teaches that blood cells represent the most accessible and most readily available of human tissues and that they exist in continuous and intimate contact with the dyslipidemic plasma and their mtDNA would therefore be expected to show any damage resulting from the abnormal environment in their milieu (page 236, col. 1). Therefore, the ordinary artisan would have been motivated to have used the most accessible tissue available which allows for detection of mtDNA damage, i.e. blood/white cells. The ordinary artisan would have been motivated to have substituted blood for the human aorta tissue which was invasively obtained by Yan. A non-invasive procedure for tissue collection would have been an obvious benefit to the method of Yan. Therefore, substituting a blood sample, as taught by VenMurthy, for the aortic tissues sample of Yan would have been obvious to the ordinary artisan at the time the invention was made.

8. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of VenMurthy et al. (Acta Biochimica Polonica, Vol. 43, No. 1, pages 227-240, 1996) as applied to Claims 6, 7, 8, 9, 14, 15, 21, 23 above and further in view of Van Houten (US Pat. 5,989,816, November 23, 1999).

Neither Yan, nor VenMurthy specifically teach treating DNA with FAPY glycosylase prior to PCR amplification.

Van Houten however teaches method for detection DNA damage by detecting 8-oxo-deoxyguanosine (8-oxo-G-lesion) using FAPY glycosylase. Van Houten specifically teaches that the assay efficiently detects most forms of base damage and DNA single and double strand breaks. The FAPY converts the 8-oxo-dG strand break with a glycosylase/endonuclease from E. coli. The DNA was used to determine the number of lesions/17.7kb.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the mtDNA damage methods of Yan in view of VenMurthy with the teachings of Van Houten. Van Houten specifically teaches that to directly measure some DNA lesions it is necessary to first convert the 8-oxodG to a strand break with a glycosylase/endonuclease. Therefore the ordinary artisan would have recognized that strand damage methods with 8-oxodG requires treatment with FAPY to determine the amount of damage. Thus, the ordinary artisan must treat the DNA with FAPY glycosylase prior to PCR amplification for detection of 8-oxo-G lesions.

Conclusion

9. **Claims 6-9, 14-23 are rejected.**

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.



Jeanine Goldberg
Primary Examiner
February 14, 2005